Methods of Preparation of dehydro-thio-p-toludine and 2 (p-aminophenyl)benzothiazole; a study of some derivatives of the former.

DISSERTATION

SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN THE FACULTY OF PURE SCIENCE OF COLUMBIA UNIVERSITY

By

F. D. SNELL, B.S., A.M.

NEW YORK CITY

1923

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ACKNOWLEDGMENT

The author wishes to express his thanks for and appreciation of the most valuable and sympathetic aid given by Marston Taylor Bogert at whose suggestion and under whose direction this research was undertaken.

Methods of Preparation of dehydro-thio-p-toludine and 2 (p-aminophenyl)benzothiazole; a study of some derivatives of the former.

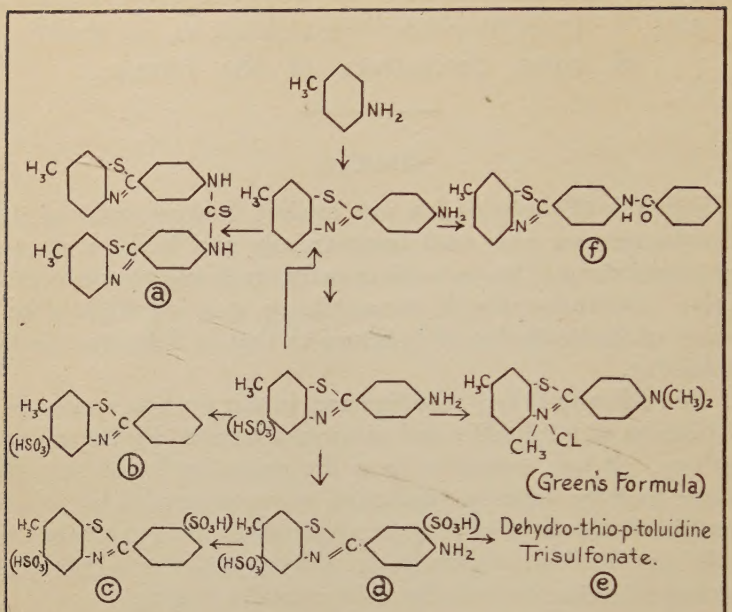
Abstract

Dehydro-thio-*p*-toluidine was studied because some of its compounds are now used commercially and because of the potential value of its derivatives as dyestuffs and pharmaceuticals. 2(*p*-aminophenyl) benzothiazole was investigated because of its similarity of structure to that of dehydro-thio-*p*-toluidine.

The dehydro-thio-*p*-toluidine used in this work was prepared by fusion of *p*-toluidine and sulfur as described by Green and others. It was separated from the primuline formed at the same time by vacuum distillation as recommended by Green and in furtherance of this the vapor pressure curve between 295° and 360° was determined. Other syntheses of dehydro-thio-*p*-toluidine were studied with negative results.

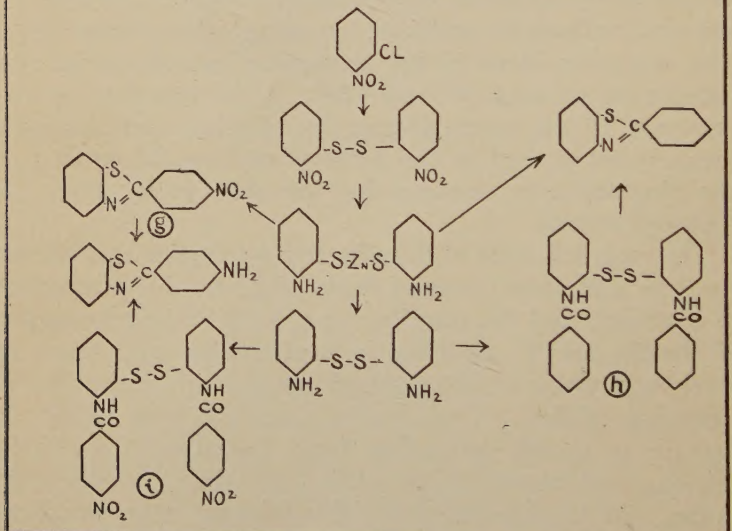
Dehydro-thio-*p*-toluidine monosulfonate was prepared by known methods and a critical study made of these methods. Certain discrepancies in the literature as to procedure were cleared up by the preparation of both a di- and trisulfonate by the usual sulfonation methods, but using higher temperatures. The solubility curve of the ammonium monosulfonate was determined between 20° and 100°. Light was shed on the structure of the monosulfonate by showing that the sulfo group is not located on the 2-phenyl nucleus and on that of the disulfonate by showing that one sulfo group is on the 2-phenyl nucleus.

The monosulfonate of dehydro-thio-*p*-toluidine was hydrolyzed by acid under pressure to give dehydro-thio-*p*-toluidine in good yield and this reaction was applied to the preparation of Thioflavine T, resulting in a simplified procedure. A study was made of the reported methods of production of Columbia Yellow. Unsuccessful attempts were made to prepare a pseudo primuline from benzal-dehydro-thio-*p*-toluidine and benzoyl-dehydro-thio-*p*-toluidine by fusion with sulfur. Di-dehydro-thio-*p*-toluidine-thiourea was prepared and its reactions to produce simpler dithioureas studied.



Flow Sheet

Letters refer to Abstract.



A simple method of production of *o*-aminothiophenol derivatives was worked out in which the zinc salt of the above was heated with benzoyl chloride or a substitued benzoyl chloride. The same results were also attained through oxidation of the thiophenol salt to the disulfid, condensation with benzoyl chloride or a substituted benzoyl chloride and reduction of the disulfid, resulting in the closing up of the cycle to give the same compounds as by the first method.

The following new substances were prepared in the course of the work:

(a)—Di-dehydro-thio-*p*-toluidine-thiourea
(b)—2-Phenylbenzothiazole monosulfonate
(c)—2-Phenylbenzothiazole disulfonate
(d)—Dehydro-thio-*p*-toluidine disulfonate
(e)—Dehydro-thio-*p*-toluidine trisulfonate
(f)—Benzoyl-dehydro-thio-*p*-toluidine
(g)—2(*p*-Nitrophenyl)benzothiazole
(h)—Bis(*o* benzoylaminophenyl)disulfid
(i)—Bis(*o p*-nitrobenzoylaminophenyl)disulfid

Introductory and Historical

History of dehydro-thio-p-toluidine

By the reaction of *p*-toluidine and sulfur at 140-145° in the presence of litharge Merz and Weith[3,4] observed the formation of thiotoluidine. They found resins containing high percentages of sulfur to be simultaneously formed, especially if the temperature went unduly high. Mandelbaum [95] studied the same reaction further and did not find dehydro-thio-*p*-toluidine present in the resins produced as described above.

The first case recorded of production of dehydro-thio-*p*-toluidine is a German patent[13] which claimed the production of a new "thio-*p*-toluidine" by heating *p*-toluidine with sulfur at 175-185° until no more H_2S is evolved (24 hours). The product is described as crystallizing from alcohol in golden yellow flakes with a melting point of 175° (uncor.). The formula claimed ($C_{14}H_{16}N_2S$) differs from the correct one ($C_{14}H_{12}N_2S$) only by having four more hydrogen atoms. They observed that only half the nitrogen could be diazotized.

A. G. Green must have been working in the same field at

that time or very soon afterwards since in 1887 the firm of Brooke, Simpson & Spiller introduced a dye, primuline, which is a higher member of this series. This introduced the use of ingrain dyes in which primuline is diazotized and developed on the fiber to be dyed.[19] In 1888 a patent[22] claimed separation of a "thiotoluidine" from the crude melt of *p*-toluidine and sulfur heated for 24 hours at 190°, and another[23] gave a melt much like that used in this work. In both cases the materials obtained were to be used for sulfonation. In the case of melts of *p*-toluidine and sulfur the conditions described usually depend on the purpose for which they are to be used, some to obtain pure dehydro-thio-*p*-toluidine with primuline base a by-product, and some for sulfonation to give the maximum yield of primuline dye or of dehydro-thio-*p*-toluidine monosulfonate.

Other firms investigated the nature of the dye marketed as primuline (not patented) and sold the same product under other names.

Jacobson named dehydro-thio-*p*-toluidine[27] and showed that it could be produced by reduction of primuline by HI and red phosphorus. He confirmed the observation[13] that half of the nitrogen present could not be diazotized.[28] He made the phenol and its acetyl derivative[29] and by molecular weight determination showed that the molecule contained only two benzene nuclei. His product melted at 191° (uncor.). The yield claimed is under 25%.

Gattermann[31] published the distinction between primuline base and dehydro-thio-*p*-toluidine which had been worked out by Duisberg and Pfitzinger in unpublished work. He showed[32] the molecular weight of dehydro-thio-*p*-toluidine to conform to $C_{14}H_{12}N_2S$. His method of preparation offers nothing original. He diazotized in boiling alcohol to remove one amino group and obtained 2-phenyltoluthiazole.[33] This he treated with acetyl chloride but recovered it unchanged. In spite of that he still considered it possible that dehydro-thio-*p*-toluidine was a derivative of stilbene or diphenyl. Anschütz and Schultz[34] offer nothing new.

Late in 1889 Green published articles[36,44,50] covering his researches. He confirmed many of the observations of Jacob-

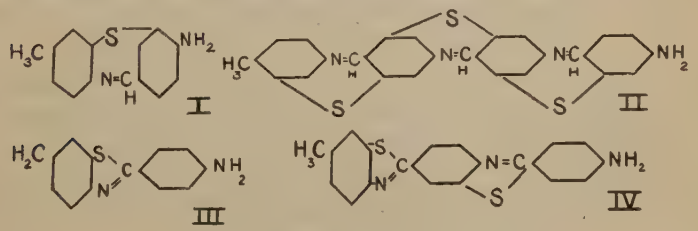
son[27] and of Gattermann.[31] He recommended distillation and crystallization from amyl alcohol to obtain a pure product. He produced the monosulfonate[38, 46, 50] (which will be discussed later), diazo chloride, acetyl derivative, dimethyl derivative, and trimethyl ammonium iodide and chloride. The latter is the dye, Thioflavine T.

Two modifications of the usual procedure in fusion were patented about the same time, one[51] claimed the production of dehydro-thio-*p*-toluidine by heating *p*-toluidine with acid sulfites or sulfurous acid at temperatures varying from 170-250° with or without the addition of sulfur. The second[52] claimed 70% yield of the same product from *p*-toluidine and sulfur at 210° in the presence of napthalene as a temperature regulator and purifier. No criterion of purity mas mentioned.

Paul[63] has described a commercial procedure similar to that of the Casella patent[52] using *p*-toluidine in excess or napthalene as temperature regulator. A German patent[66] claimed the production of dehydro-thio-*p*-toluidine from *p*-aminobenzyl-*p*-toluidine by fusion with sulfur. Jansen[73] described a commercial procedure for a melt to be sulfonated to give mainly primuline. Fierz[84] described a melt to be used for sulfonation.

M. Meyer[91] investigated the purification of dehydro-thio-*p*-toluidine by vacuum distillation and reported yields of under 20%. He found the preparation of a pure product by the Casella patent[52] unsatisfactory.[87] He found that dehydro-thio-*p*-toluidine could be purified from a small amount of *p*-toluidine by one crystallization.[88] He reported the melting point of a very pure sample as 194.8° (cor.).[91]

Morgan and Webster[86] uscd dehydro-thio-*p*-toluidine as an amine having a very stable diazo compound to produce syn- and anti-diazo chlorides stable at ordinary temperatures.

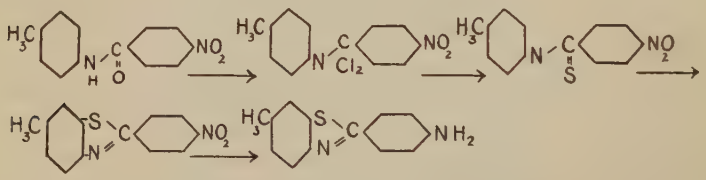


Structure of dehydro-thio-p-toluidine

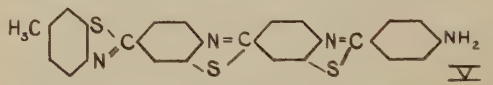
Green[39, 48, 50] thought that dehydro-thio-*p*-toluidine had Formula I because it formed an unstable bromine compound. He concluded that primuline had at least 28 carbon atoms in the molecule because it was obtained by heating dehydro-thio-*p*-toluidine with sulfur, and gave as its structure Formula II.[49]

Pfitzinger and Gattermann[40] published a proof that dehydro-thio-*p*-toluidine had Formula III, the present accepted constitution. They repeated[41] Jacobson's synthesis[15] of 2-phenyl-toluthiazole. By KOH fusion they obtained benzoic acid from the same amide-free base produced from dehydro-thio-*p*-toluidine. The other portion of the compound gave on fusion[42] 2-amino-5-methylthiophenol which was identified in the form of the diazosulfid.[35] The disulfid was also formed as a method of identification. In a similar way by KOH fusion of dehydro-thio-*p*-toluidine they obtained *p*-aminobenzoic acid and the above diazosulfid. Studies of the structure of primuline were less conclusive but the structure was stated[43] as Formula IV, or a higher member of the same type, a structure still accepted.

The proof of the structure of dehydro-thio-*p*-toluidine was completed by Gattermann and Neuberg[57] by a synthesis from *p*-nitrobenzoyl chloride and *p*-toluidine as is summarized below:



Part of the synthesis was also carried out as follows:[58]

* 

V

The dehydro-thio-*p*-toluidine was distilled before crystallization to purify it. The results here obtained are marred by the fact that they did not purify and analyze two compounds of their series.

Green, in Thorpe's Dictionary[75] gives a resume of the results

* See Errata at end of dissertation.

reported in his earlier papers with some new material. He concludes[76] that commercial primuline consists almost entirely of the monosulfonate of the condensation product of dehydro-thio-*p*-toluidine with one mole of *p*-toluidine (IV) with possibly a small amount of the next higher member of the series (V). * He also found more complex bases by heating 3 atoms of sulfur with one mole of *p*-toluidine.

Production of dehydro-thio-p-toluidine

Dehydro-thio-*p*-toluidine was prepared by the fusion method and separated from primuline by vacuum distillation. A period of 4-6 hours' heating, after raising the temperature rapidly to 240-250°, was found most satisfactory. Under those conditions much *p*-toluidine remains unchanged and may be recovered but the amount of primuline formed is smaller proportionally than with a longer period of heating. A pure product (m.p. 193°, cor.) was consistently obtained in yields of over 50%, correcting for the *p*-toluidine recovered. Under these conditions little if any thiotoluidine is produced.

Fierz[84] specifies powdered roll sulfur rather than flowers, but comparative experiments show that results by distillation are not affected by the choice. The yields from *p*-toluidine of pure, practical, and technical grade were approximately the same.

The distillation of dehydro-thio-*p*-toluidine from a commercial crude melt was found unsatisfactory.

M. Meyer[88] reported the boiling point of dehydro-thio-*p*-toluidine to be 345° at 35 mm. and Green,[37, 45, 50, 75] 434° (uncor.) at 766 mm. Since considerable amounts of dehydro-thio-*p*-toluidine were to be made by distillation a series of points between 295° and 370° were determined on the vapor pressure-temperature curve.

Although there is no clean-cut method of separation of dehydro-thio-*p*-toluidine from primuline by extraction it seemed best to make a survey of the extraction methods reported in order that a future investigator who desired to make a small amount of dehydro-thio-*p*-toluidine such as 5 or 10 g., might find a method other than distillation reported in detail. The Casella patent[52] was tried out on a small scale and found unsatisfactory although a yield of 3 to 5% of pure

* See Errata at end of dissertation.

product can be obtained by this method with considerable difficulty. By extraction of a crude melt with concentrated HCl [13] the results were unsatisfactory but if extraction is with hot diluted HCl (2 H_2O : 1 HCl) [30] a pure product can be obtained.

A melt made with excess *p*-toluidine, following Green's directions, [37, 45] yielded dehydro-thio-*p*-toluidine by extraction with a mixture of equal volumes of benzol and petrolic ether. The loss is excessive except for small scale work.

M. Meyer [89] investigated the results of fusion of *p*-nitrobenzal-*p*-toluidine with sulfur, with the expectation that either dehydro-thio-*p*-toluidine itself or the corresponding nitro derivative, 2 (*p*-nitrophenyl) toluthiazole would be formed. The results were unsatisfactory. It was thought that if the nitro group were first reduced and the fusion then carried out the reaction might work out satisfactorily.

Strakosch, [6] Paal [18, 21] and others [20, 64, 67] have investigated *p*-aminobenzyl-*p*-toluidine with many contradictory results.

Acid and alkaline reduction of *p*-nitrobenzal-*p*-toluidine yielded a red resinous material which on fusion with sulfur gave no dehydro-thio-*p*-toluidine. Fusion of the nitro compound with sodium sulfid and sulfur gave only the resin mentioned above. This resin appears similar to a product described in the literature as *p*-aminobenzyl-*p*-toluidine. [62, 66]

The preparation of *p*-aminobenzyl-*p*-toluidine has been covered by German patents. [62, 66] The product is claimed to react on fusion with sulfur to give dehydro-thio-*p*-toluidine. Prepared according to the above patent it was found that *p*-toluidine, not removed by the method of purification claimed, was the source of the dehydro-thio-*p*-toluidine and that when that had been removed no reaction occurred on fusion with sulfur.

Condensation of an *o*-aminomercaptan with *p*-nitrobenzoyl chloride also offers a promising synthesis. This was investigated in the form of the more easily obtainable *o*-aminothiophenol to give 2(*p*-aminophenyl)benzothiazole rather than by use of the corresponding aminothiocresol to give dehydro-thio-*p*-toluidine.

Sulfonation of dehydro-thio-p-toluidine

The sulfonation of dehydro-thio-*p*-toluidine with fuming H_2SO_4 under 50° results in a monosulfonate. A similar sulfonate of primuline base is used in the form of the sodium salt as the dye primuline. The sodium salt of dehydro-thio-*p*-toluidine monosulfonate is of technical importance in the preparation of the dye Columbia Yellow (see below). Since the sulfonates of both dehydro-thio-*p*-toluidine and primuline are of technical importance, instead of separating them and then sulfonating, it is often more convenient to sulfonate the mixed bases and then separate. In practically all cases this separation depends on the fact that the ammonium salt of dehydro-thio-*p*-toluidine monosulfonate is relatively insoluble in water as compared with the ammonium salt of primuline sulfonate.

The first case of sulfonation of dehydro-thio-*p*-toluidine is that of a German patent[22,24] on the sulfonation of "thio-*p*-toluidine". The first case of sulfonation for separation of the mixed bases is recorded in a "pli cachete"[72] entitled "Notes on Primuline" deposited on November 2, 1889, by Charles Dreifus of the Clayton Aniline Company, and first published in 1911.

Green [38,47,77] gvies methods for sulfonation of dehydro-thio-*p*-toluidine. Molecular weight determinations were made More modern details are given by Jansen[73] and probably represent, more or less, modern practice on an industrial scale. Details given by Fierz[84] differ in some particulars from those already mentioned.

It is to be noted that Jansen[74] recommends that the sulfonation be stopped as soon as a sample is soluble in alkali and says that over-sulfonation may occur. Fierz[84] recommends the opposite, that the material be kept warm for two hours after a sample shows complete sulfonation.

The ammonium monosulfonate of dehydro-thio-*p*-toluidine was prepared following the directions of the latter two references.

The effect of passing dry ammonia gas into a saturated aqueous solution of dehydro-thio-*p*-toluidine ammonium monosulfonate was found to be negligible.

The solubility of the ammonium monosulfonate was deter-

mined over the range 18.1-100° because of its practical importance in the purification of the salt by crystallization. The only comparable results are those of Dreyfus and Hall[71] who found 7 g. per liter at 14.6° as compared with our result of 1.3 g. by extrapolation from 18.1°.

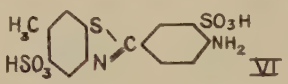
A patent [79, 80] has been obtained on another sulfonate of dehydro-thio-*p*-toluidine and a disulfonate by a process in which dehydro-thio-*p*-toluidine is treated with the calculated amount of sulfuric acid monohydrate and heated to dryness in a vacuum at 235-250°. The formation of a disulfonate by the action of fuming H_2SO_4 on the monosulfonate made by their "baking" process is also claimed.

It was hoped that a disulfonate might be formed in the wet way by using a higher temperature, the formation of which might explain Jansen's reference[74] to over-sulfonation of the crude melt. By sulfonation at 100° with excess of 50% fuming HS_2O_4 such a disulfonate was produced. Similarly by sulfonatino at 200° a trisulfonate was produced.

The anhydrous ammonium salts of the three sulfonates show an interesting gradation of color. The monosulfonate is very light yellow, the disulfonate is a deeper yellow, the trisulfonate a still deeper yellow.

Structure of the sulfonates

The only reference to the location of the sulfo groups in dehydro-thio-*p*-toluidine sulfonates is in the patent on the "baking" process [77, 78] previously mentioned, which says that the structure is probably Formula VI, without offering proof.



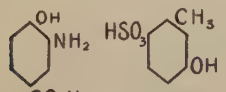
VI

Bogert and Abrahamson[94] have found that the nitro group in 2-phenylbenzothiazole is located in position 6. It seems probable from similarities of structure that the sulfo group in the above compound is located on the same nucleus although position 6 is occupied by the methyl group. As further evidence it was found that on nitration of dehydro-thio-*p*-toluidine[61] the nitro group was on the same nucleus as the methyl group.

The location of the first two sulfo groups was investigated. Distillation of dehydro-thio-*p*-toluidine monosulfonate with soda-lime yielded aniline. Fusion with alkali gave *p*-aminobenzoic acid. Dehydro-thio-*p*-toluidine monosulfonate was diazotized to give a diazo compound, stable at ordinary temperatures. On decomposition with pure amyl alcohol this yielded 2-phenyltoluthiazole monosulfonate. Fusion of this with alkali gave benzoic acid. From these we may conclude that the sulfo group ih on the benzothiazole portion of the compound. Attempts to locate this group by hydrolysis of the monosulfonate in 99.5% alcohol with KOH in the manner used by Rassow, Döhle, and Reim[83] in the case of benzothiazole sulfonates were unsuccessful.

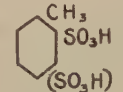
Dehydro-thio-*p*-toluidine disulfonate was similarly diazotized, dried and boiled with amyl alcohol. The product, 2-phenyltoluthiazole disulfonate on fusion with alkali yielded phenol. This would indicate that the second sulfo group enters on the 2-phenyl nucleus. The isolation of the oxybenzoic acid was unsuccessful.

Post[12] found that sulfonation of *o*-aminophenol gives the sulfo group in position 4 (VII); Claus and Kraus[17] that sulfonation of m-cresol gives the sulfo group in position 6 (VIII). Sulfonation of toluene gives principally the ortho and para compounds[99] (IX). These agree with the relative position we have assigned to the sulfo group (X).

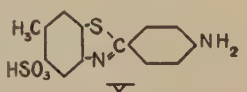


VII

VIII



IX



X

As against this it should be mentioned that Rassow, Döhle and Reim[81] found by sulfonation of benzothiazole three isomeric sulfonates, 4, 5 and 7, but the amounts of each are not given. Sulfonation of quinoline gives a sulfo acid with the sulfo group in a position corresponding to position 7 in our formula.[82] Sulfonation of *p*-toluidine gives the sulfo group either *o*- or *m*- to the methyl, depending on the conditions.[7] Low temperature and low concentration of SO_3 favor meta substitution. The first sulfo group has been tentatively

assigned to position 5 pending further evidence of its location.

With regard to the second sulfo group, the second position occupied in sulfonation of aniline[1] is ortho to the amino group. The principal product on sulfonation of benzoic acid[8] is the meta sulfonate with little of the para. Our position agrees with both of these observations so the second sulfo group has been tentatively assigned to a position ortho to the amino group (VI).

Hydrolysis of dehydro-thio-p-toluidine

It was hoped that by heating the monosulfonate of dehydro-thio-*p*-toluidine with HCl under pressure the sulfonic group might be split off and dehydro-thio-*p*-toluidine regenerated. Since the separation of dehydro-thio-*p*-toluidine monosulfonate from primuline is much more readily carried out on a large scale than the separation of dehydro-thio-*p*-toluidine from primuline base this would offer a practical method of production of dehydro-thio-*p*-toluidine. Such an hydrolysis was obtained at 200-220° with 10 parts of concentrated HCl in nearly quantitative yield.

Thioflavine T is a commercially important yellow dye produced by methylation of dehydro-thio-*p*-toluidine with methyl alcohol and methyl halide or hydrochloric acid.[25, 38, 46, 50, 54, 78] Our interest in this dye arose from the fact that, since we could produce dehydro-thio-*p*-toluidine from dehydro-thio-*p*-toluidine monosulfonate, the reaction might work in an analagous manner to produce Thioflavine T if methyl alcohol were added to the mixture of dehydro-thio-*p*-toluidine monosulfonate and hydrochloric acid. In addition to the original method of direct methylation there is another patent[26] which claims that by use of alkylation methods which permit of a higher temperature, with dehydro-thio-*p*-toluidine sulfonate, the sulfo group is split off and thioflavine sulfate produced. The following is the only example covering this claim.

"34.5 kg. of the sodium salt of the sulfo acid of dehydro-thio-*p*-toluidine (m.p. 193°) are heated with 100 kg. methyl alcohol (or a like amount of ethyl or amyl alcohol), for ten hours at 160-170°. The contents of the pressure vessel consist of the sulfuric acid salts of thioflavine, which are separated according to the method of patent 51,738." [25]

It was found that Thioflavine T was not produced by following these directions but only a white water-soluble compound. If, however, we add hydrochloric acid to the specified reagents and carry out the reaction at 200-220° a yellow dye is produced which possesses the properties of Thioflavine T made by methylation of dehydro-thio-*p*-toluidine.

Derivatives of dehydro-thio-p-toluidine

Portions of the sodium salt of dehydro-thio-*p*-toluidine monosulfonate were oxidized with sodium hypochlorite prepared from calcium hypochlorite and sodium carbonate, lead dioxide paste, alkaline potassium ferricyanide,[56] and best, an accurately titrated solution of sodium hypochlorite[85] made by passing chlorine into sodium hydroxide.

Dehydro-thio-*p*-toluidine condenses readily with benzaldehyde to give benzal-dehydro-thio-*p*-toluidine.[91] It was thought that if benzal-dehydro-thio-*p*-toluidine were fused with sulfur in the manner of production of 2-phenylbenzothiazole from benzalaniline[53, 56, 94] the analagous reaction might be expected to take place, forming a primuline-like product which we have called pseudo orimuline.

The melt obtained using proportions according to the above equation was carefully examined but evidence obtained showed that the reaction went on to only a small extent if at all.

Benzoyl-dehydro-thio-*p*-toluidine was prepared by condensation of benzoyl chloride and dehydro-thio-*p*-toluidine in the hope that by fusion with sulfur it might yield pseudo primuline in a manner analagous to that used for the preparation of benzothiazole from benzanilide.[11, 93] A fusion with sulfur in theoretical proportions gave a material which was insoluble in any solvent tried and which charred above 350°. It did not seem probable that this was pseudo primuline so the residue was not further investigated.

An attempt to condense dehydro-thio-*p*-toluidine with hydroquinone[60] and from this condensation produce a dye similar to hydrone blue[69, 70] was also unsuccessful.

Since dehydro-thio-*p*-toluidine is a primary amine it was thought that it might condense with carbon disulfid to give di-dehydro-thio-*p*-toluidine thiourea. This product was pre-

cipitated by long boiling of dehydro-thio-*p*-toluidine and carbon disulfid in alcohol or acetone solution. Its instability is shown by the fact that when boiled for three hours with alcohol or toluene and a large excess of aniline it is decomposed to give dehydro-thio-*p*-toluidine and thiocarbanilid. Similar results were obtained with *o*-toluidine although 20 hours' boiling was required.

Derivatives of o-aminothiophenol

o-Aminothiophenol is described in the literature as made from oxalaminothiophenol[11] or from 2-phenylbenzothiazole[16], by fusion with KOH. Vanino[96] recommends the latter method for its production. The yields claimed by the first method were low and the starting materials are such as to make the latter expensive. Accordingly a new and inexpensive synthesis was sought.

Wohlfahrt[68] described the production of dinitrophenyldisulfid from both *o*- and *p*-chlornitrobenzol. Reduction of the *o*-dinitro compound with tin and HCl was unsuccessful but it was found that when dissolved in glacial acetic acid and boiled with a large excess of zinc, dust,[68a] reduction occurred and on cooling the zinc salt of *o*-aminothiophenol crystallized out in good yield. Reduction also occurred on standing in the cold for several hours. Similar results were obtained by filtration of the hot acetic acid solution after reduction, into two volumes of water, thus precipitating the zinc salt,—also in good yield.

By heating this zinc salt with benzoyl chloride, 2-phenylbenzothiazole was obtained in good yield and very pure form. In a similar way *p*-nitrobenzoyl chloride gave 2(*p*-nitrophenyl) benzothiazole which on reduction with tin and HCl gave 2(*p*-aminophenyl)benzothiazole.[71]

By dissolving the zinc salt of *o*-aminothiophenol in ammonia it is readily oxidized by passing air through to give the corresponding disulfid. This is readily benzoylated to give bis (*o*-dibenzoylaminophenyl)disulfid which by reduction with tin and boiling HCl gives 2-phenylbenzothiazole (rosenkörper) in pure form with good yield.

The corresponding reaction with *p*-nitrobenzoyl chloride gives bis(*o p*-nitrobenzoylaminophenyl)disulfid which, similarly

reduced yields the same 2(*p*-aminophenyl)benzothiazole.[71]

Experimental

1. Dehydro-thio-p-toluidine

Method A. From p-toluidine and sulfur by fusion and vacuum distillation

The preparation of dehydro-thio-*p*-toluidine by the distillation method was investigated using the special flask designed by M. Meyer.[90] The apparatus used for the distillation is shown in the accompanying drawing (see Fig. I). A is a 500 cc. pyrex flask fused to B, a 250 cc. pyrex flask, by a six to eight inch pyrex tube of 1½ cm. inside diameter. This gives a convenient form of apparatus which is firm enough so that it may be easily handled without danger of breakage and may be used for many successive distillations. The flask A must have a stricture in the neck to hold a pad of asbestos which was found to be sufficient to protect the rubber stopper from the heat in the flask. A thermometer may be inserted. In later work after experience had been gained the thermometer was omitted, eliminating

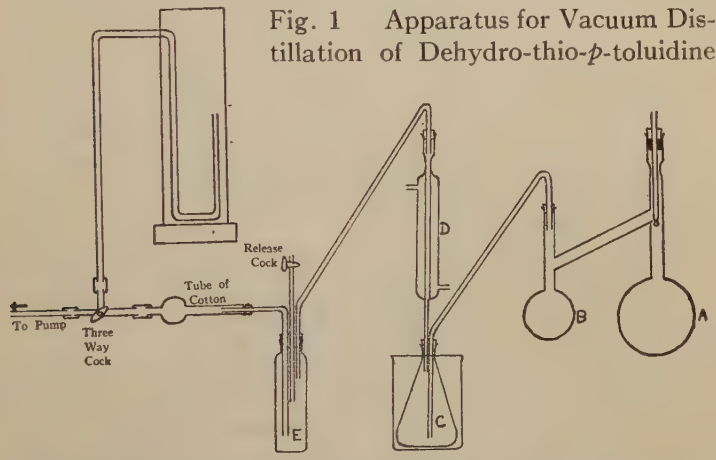


Fig. 1 Apparatus for Vacuum Distillation of Dehydro-thio-*p*-toluidine

one possible source of leakage. The temperature in flask B is not sufficient to affect a rubber stopper. C is an auxiliary flask added to collect the *p*-toluidine distilled over from B. This is cooled by standing in a beaker of water. A Liebig condenser D is attached to it to prevent *p*-toluidine being carried further. E is a safety bottle which gives a means of reducing the pressure in case of foaming in A and at the end of the distillation. After the technique had been developed it was used only to release the pressure at the end of a run. A calcium chloride tube of cotton served further to prevent solid passing through to the pump, although nothing collected in it.

A bunsen valve (not shown) prevented water backing up into the apparatus. All joints were made air tight by sealing with a mixture of fine asbestos fibers and sodium silicate. The stopper and thermometer should also be protected from heat by an external sheath of asbestos paper extending from the stricture to above the stopper.

The melt used was approximately that found most satisfactory for preparation of dehydro-thio-*p*-toluidine by several previous investigators[30, 32, 34, 36, 44, 52, 91] using less sulfur than is used when primuline is the desired product. 110 g. of *p*-toluidine (Eastman Kodak Co. practical, m.p. 42°) were melted on a metal bath with 60 g. of sulfur (flowers) at 150° using a 500 cc. flask with a wide bore air condenser. Identical results within the experimental error were obtained on distillation, first when the melt was heated slowly to 210° and kept there until evolution of H_2S ceased (20 hours), second, when it was later raised to 250° with a furthee evolution of small amounts of gas, and third, when it was rapidly raised to 250° and kept there 4 to 6 hours. If the melt were kept at 250° for morr than six hours, at which time evolution of H_2S had not quite ceased, the yield of dehydro-thio-*p*-toluidine did not change but the *p*-toluidine recovered was much reduced. A 4 to 6 hour period of heating was therefore adopted.

It was not found advisable to cool and powder the melt but it was poured directly into flask A through a wide funnel which had been previously warmed with a free flame. This eliminated troublesome melting and cooling.

In distillation the first material goes over at about 100° and 30 mm. This was identified by melting point and crystalline form as *p*-toluidine. When this had all gone over into B and the temperature of A had risen to 200°, B was heated with a free flame and the *p*-toluidine distilled over into C for later recovery.

Distillation of dehydro-thio-*p*-toluidine takes place readily at 304° and 20 mm. The condensation on the neck and sides of A is prevented by warming with a free flame, manipulated by hand, and foaming is prevented by leaving a cool area of the flask just above the boiling liquid. Distillation is best stopped before the last of the dehydro-thio-*p*-toluidine goes over, for two reasons: First, the tendency to foam becomes greater as more of the dehydro-thio-*p*-toluidine is distilled off and second, it leaves the residue more fluid at the end. The vacuum was then broken and the residue from A poured onto watch glasses. The cleaning of A after each run was thus eliminated.

The product obtained in B is almost pure dehydro-thio-*p*-toluidine. It solidifies while distillation is going on to a yellow to red cake. For small amounts this might be extracted with alcohol but for any large production this is not at all practicable. After pouring the residue from A, B was heated over a free flame to melt the material contained and this was poured onto a watch glass to cool. The flask was then ready for use again.

After a series of runs the residue in C, which was yellow to brown, was melted out with warm water and steam-distilled to recover as much

p-toluidine as possible. The *p*-toluidine recovered was better in quality than the starting material as shown by the melting point, 44°, of a representative sample (starting material 42°). The residue remaining after steam distillation was largely dehydro-thio-*p*-toluidine carried over into C by the rapid stream of *p*-toluidine vapor, as was shown by the fact that a sample dissolved in alcohol gave a greenish yellow fluorescence and crystallized after standing several days to give impure crystals of dehydro-thio-*p*-toluidine, m.p. 189° (cor.). To explain this it must be recalled that B was not washed with alcohol after each experiment but that the sides were coated with a thin layer of dehydro-thio-*p*-toluidine left in pouring out the molten product. The presence of any considerable amount of thiotoluidine in the crude melt is therefore impossible since this residue was only four grams from a series of eleven runs.

From the average of a series of runs the yield of distilled product before crystallization was 52.7% but the corrected yield, allowing for the *p*-toluidine recovered was 72%. Recrystallized to a product melting at 194° (cor.), the yields were 38.1% and 52% respectively.

Results using roll sulfur instead of flowers[84] were not found to vary beyond the experimental error.

A batch using carefully purified *p*-toluidine (m.p. 44.5°) instead of "practical" did not differ in yield from those obtained with the usual grade. The distilled product before recrystallization was slightly darker and harder, probably an accidental variation. The use of technical *p*-toluidine also gave as good results.

Distillation to remove the last possible trace of dehydro-thio-*p*-toluidine gave but little increase in the yield, 2 to 3%.

To summarize, the conclusion was reached from these results that the most satisfactory procedure was to heat for 4 to 6 hours at 240-250°, recover unchanged *p*-toluidine by distillation into C for later purification, and distil the main part of the dehydro-thio-*p*-toluidine but not all, removing the distillate and the tarry residue by pouring onto watch glasses as soon as the vacuum is broken.

An attempt was made to use a commercial crude melt, the composition of which was unknown, in place of that described above. It was obtained in a finely powdered form. When a flask was charged with it and an attempt made to distil, it melted to a viscous mass from which dehydro-thio-*p*-toluidine could be distilled only with great difficulty. From a batch of 150 g. it was practicable to distil about 25 grams of dehydro-thio-*p*-toluidine but the flask had to be carefully watched to prevent foaming over. The use of this material was abandoned because the residue left in the flask could not be poured out but must be dissolved out with H_2SO_4 or napthalene after each use. Adopting the procedure in which the melt was not heated until all *p*-toluidine had reacted and observing the other precautions mentioned these difficulties are practically eliminated.

The distilled dehydro-thio-*p*-toluidine dissolves readily in alcohol to the limit of its solubility, which is moderate, and crystallizes on cooling as beautiful yellow needles of m.p. 193-194° (cor.). The amount of impurity

is such that it was found possible to crystallize three successive amounts from the same alcohol before the quality of the product would be lowered. If the alcohol from which crystallization is carried out is dark with impurities and if the cooling is very slow the dehydro-thio-*p*-toluidine may be obtained in long lustrous needles which are yellow to transmitted light but exhibit a beautiful vari-colored fluorescence, green, yellow, red, and brown to reflected light, especially artificial light. The product so obtained usually melts (193°, cor.) about a degree lower than the pure product.

A hot solution of dehydro-thio-*p*-toluidine in strong HCl deposits a small amount of shining deep-yellow plates on cooling which are probably a hydrochloride. If these are added to water they turn lighter and on neutralization with NH_4OH become white. Both dehydro-thio-*p*-toluidine and its compounds exhibit a property often found among sulfur compounds and mentioned by Hofmann for other compounds, of causing an irritation of the skin, very much like eczema.

Since considerable amounts of dehydro-thio-*p*-toluidine were to be made by the distillation method the vapor-pressure temperature curve was determined over a range from 295° to 370°. For this purpose a large pyrex test tube containing 25 g. of dehydro-thio-*p*-toluidine (m.p. 194°, cor.) with the lower part immersed in a metal bath was connected to the manometer and safety bottle through a two-hole rubber stopper. The upper part of the test tube was strictured as previously recommended for the flask A. The other hole of the rubber stopper admitted a thermometer with its bulb just above the surface of the liquid. When the bulb of the thermometer was thoroughly bathed in the vapor of the boiling dehydro-thio-*p*-toluidine the pressure was raised or lowered slowly and the temperature taken at intervals. Points were taken both ascending and descending in order that an error might not be introduced by failure to attain equilibrium. Two samples were used and the results obtained from both are in substantial agreement. The results so obtained, corrected for exposed stem, follow and are plotted in Figure 2.

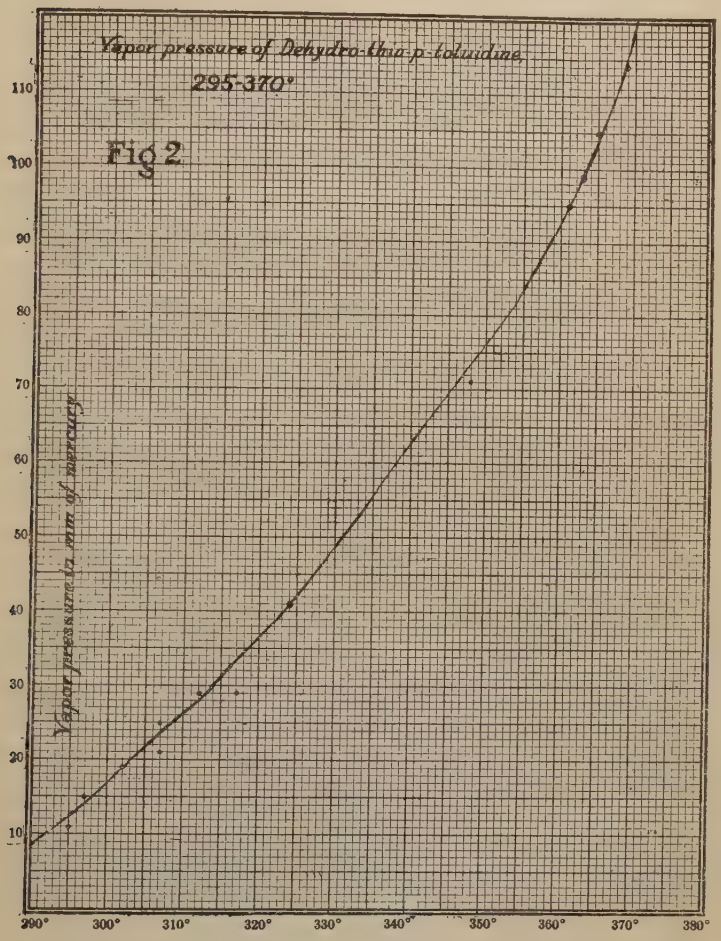
Pressure in mm.	Temp. ° C of vapor	Pressure in mm.	Temp. ° C of vapor	Pressure in mm.	Temp. ° C of vapor
11	295	29	317	85	353
15	297	41	324	95	361
19	302	45	325	99	263
21	307	55	329	105	365
25	307	71	348	115	369
29	312	75	352		

Method B. From p-toluidine and sulfur by fusion, and extraction with acid or alcohol

Extraction as a method for purification of dehydro-thio-*p*-toluidine has been repeatedly mentioned,[13, 22, 30, 32, 36, 45, 51, 52] although Green[36, 45] and

another[51] recommend distillation of the product extracted.

The investigations carried out on extraction methods were only semi-quantitative as the results in no case justified further investigation. They are here given as offering easier methods for the preparation of small amounts of dehydro-thio-*p*-toluidine such as five or ten grams, than the



distillation method which is far superior as to yield and convenience when any considerable amount is desired.

The Casella method[52] was investigated with a melt of 107 g. *p*-toluidine, 60 g. roll sulfur, and 100 g. napthalene, raising the temperature during four

hours to the boiling point of napthalene, 217°. At the end of six hours the melt was cooled and dissolved in 30% H_2SO_4, by weight. When the acid cooled the napthalene appeared on the surface as a dark crust which was removed. The dark acid solution, filtered and neutralized with NaOH, gives a yellow precipitate without sharp melting point. This will not crystallize from alcohol or acetone. By fractional extraction of this precipitate with alcohol, the first fractions would not crystallize but the latter extracts crystallized to give an impure product. Recrystallized from acetone or alcohol it melts at 192° (cor.). Precipitation of the dehydro-thio-*p*-toluidine from sulfuric acid solution by dilution with water did not prove satisfactory, as the product was slimy and would not dry.

Investigation by this method omitting the napthalene and using different temperatures gave similar results.

Twenty-five grams of dry crude melt (see A) were extracted with 100 cc. concentrated HCl,[13] filtered through glass wool and diluted with water. Only a small amount of tarry residue remained undissolved and the product obtained on dilution gave no better results with alcohol than the untreated melt.

Twenty-five grams of the crude melt were extracted with 250 cc. concentrated HCl and 500 cc. water.[30, 36, 45, 51] When filtered and diluted with 1500 cc. water a light yellow product was obtained. Further extraction of the melt with more acid of the same concentration showed that extraction was not complete. The product so obtained dissolves in alcohol to give a light yellow fluorescent solution and crystallizes with difficulty. The product is obtained pure only by several crystallizations with boneblacking. A product melting at 192° (cor.) was obtained.

Ten grams of the crude melt were extracted with 100 cc. alcohol and filtered for crystallization with unsatisfactory results. The cold alcoholic solution was filtered, precipitated with ten volumes of water, and the precipitate recrystallized from alcohol with boneblacking, to give a product melting at 192° (cor.).

One hundred and ten grams of *p*-toluidine were fused with 30 g. of sulfur at 200° for six hours.[37, 45] When the melt had partially cooled a mixture of equal volumes of petrolic ether and benzol was added and filtered hot. There was left a pasty mass which became solid on evaporation of the petrolic ether. The solution deposited crystals of *p*-toluidine on cooling, identified by melting point and crystalline form. The residue was dissolved in one part of concentrated HCl to two parts of water and precipitated by dilution with two parts of water. The precipitate so obtained, boneblacked and recrystallized from alcohol, gave a product melting at 193° (cor.).

Method C. From p-aminobenzal-p-toluidine

p-Nitrobenzal-*p*-toluidine was formed by condensation of 5 g. of *p*-nitrobenzaldehyde and 3.5 g. *p*-toluidine in alcoholic solution.[14, 92] One recrystallization from alcohol gave flattened yellow needles melting at 122.5° (cor.), 7.4 g., yield 93.3%. Lowry and King[92] found the melting point to be 122.5° (cor.); M. Meyer[89], 123° (cor.).

One gram samples of the nitro compound were reduced with zinc and HCl, tin and HCl, and zinc dust and acetic acid. In each case the product obtained by rendering the deep red solution alkaline was a red amorphous material, soluble in hot alcohol, which darkens at 170° but shows no melting point. It is probably the polymerization product mentioned in German patent 99,542.[64]

Reduction in alcohol with sodium sulfid was tried following German patent 99,542[64] and gave the product described above. Reduction with ammonium sulfid[6, 18, 20, 21, 64] and with H_2S in alcoholic solution gave the same red product with much sulfur.

A one gram sample of this red amorphous substance was fused with 0.3 g. of sulfur at 200° for 12 hours, reduced with zinc and HCl and filtered. The red material was recovered but there was no evidence of the presence of dehydro-thio-*p*-toluidine.

Two grams of the nitro compound, 2 g. of Na_2S, 9 H_2O and 2 g. of sulfur fused for four hours at 200° gave active evolution of H_2S. The mass was extracted with HCl, filtered and precipitated by NH_4OH. The precipitate was soluble in alcohol and was the same red material. No evidence of dehydro-thio-*p*-toluidine was obtained. A similar fusion for one hour gave identical results.

Method D. From p-aminobenzyl-p-toluidine

Following a patent procedure[62, 66] *p*-aminobenzyl-*p*-toluidine was made from anhydroformaldehyde-*p*-toluidine,[65] *p*-toluidine, aniline, and *p*-toluidine HCl. The compound described, a deep red viscous oil with an aniline-like odor, was obtained. The amount was slightly more than that calculated for the expected product. After a time it forms a red resinous precipitate, especially if heated. Since purification from *p*-toluidine was by steam distillation a portion was heated to 250° and more *p*-toluidine obtained, identified by melting point and crystalline form. The product does not distil at 400° and 18 mm.

Portions of the product, both after removing the *p*-toluidine at 250° and without so treating were heated with the theoretical amounts of sulfur at 200° for 48 hours. Evolution of H_2S occurred in the latter but not in the former. By extraction with dilute HCl dehydro-thio-*p*-toluidine was separated from the one from which *p*-toluidine had not been distilled but none was found in the other melt.

2. Dehydro-thio-p-toluidine monosulfonate

Ten grams of pure dehydro-thio-*p*-toluidine (m.p. 193°, cor.) were sulfonated following the general directions of Green.[38, 47, 50, 77] A yield of 3 g. of pure product was obtained after several recrystallizations from dilute ammonia. Dehydro-thio-*p*-toluidine ammonium monosulfonate crystallizes in small, very light yellow, silky needles. This served as a standard with which later products might be compared.

For testing the methods of sulfonation a crude melt of 110 g. *p*-toluidine and 60 g. of sulfur heated at 240-250° for 4 to 6 hours was used, prepared by the procedure already described (Experimental 1A). Sulfonation was carried out according to the procedure recommended by Fierz.[84] Twenty-

five grams were sulfonated in 10 hours with 60 g. of fuming H_2SO_4 (50% SO_3) at 50° with results as claimed. For laboratory use it is more convenient to use 100 g. of fuming acid and get complete sulfonation in 6 hours. In either case it was allowed to stand for two hours,[84] precipitated, filtered, etc. Recrystallization was carried out according to the methods of Green[77] and of Fierz[84] with yields of 40 and 42.8% respectively, based on the amount of crude melt used. This compares with 25% reported by Fierz,[84] 29% by Jansen[74] and over 50% by Green.[77] From the filtrate a yield of 96% of primuline was obtained, compared with 80% reported by Fierz,[84] 105% by Jansen[74] and an indeterminate amount by Green,[77] all based on the amount of crude melt. Similar results with slightly smaller yields were obtained using a commercial crude melt. The sodium salt and sulfonic acid were prepared from the above salt after one more crystallization.

The ammonium monosulfonate used in later work was made from the commercial crude melt and twice recrystallized from dilute ammonia. Since its purity was essential a sample was analyzed.

Analysis. Subs., 0.3834: $BaSO_4$, 0.5286. Calc. for $C_{14}H_{16}N_3S_2O_3$: S, 18.99. Found: 18.94.

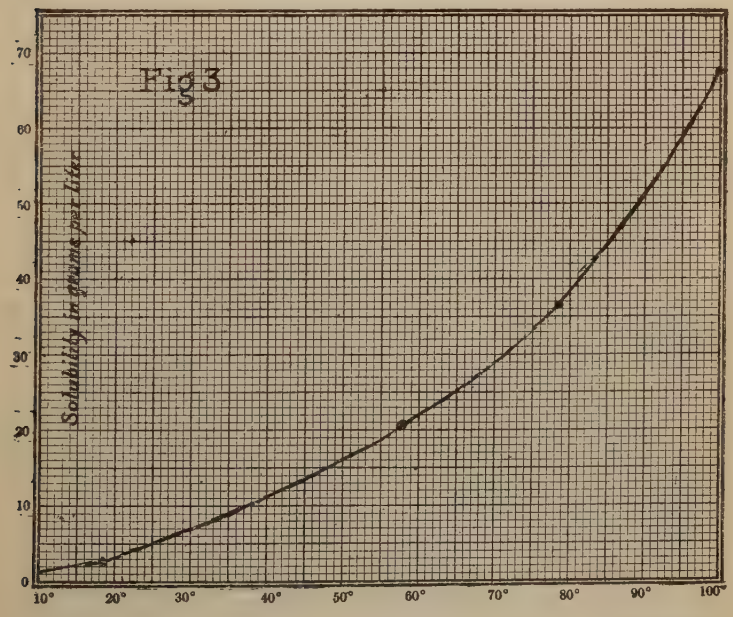
For comparison, calculated for primuline (assuming that it is the monosulfonate) $C_{21}H_{13}N_4S_3O_3$, S = 20.43%.

In order to determine the effect of excess ammonia in recrystallization, 50 cc. of saturated solution of the ammonium monosulfonate of dehydrothio-*p*-toluidine in water at room temperature were treated with dry ammonia gas from a generator, dried with lime and supplied through a thistle tube. There was ready absorption of the gas but no precipitation occurred at the time. On standing over night, covered, there was a trace of precipitate deposited. It seems probable that the solubility of the compound is little affected by the concentration of ammonia or of ammonium ion present and if at all that it acts in the way that such an ion would be expected to. That is, the degree of ionization of NH_4OH (considering that all ammonia present is NH_4OH) is much less than one per cent in so concentrated a solution and there is little effect.

Since the ammonium monosulfonate is of considerable technical importance it seemed advisable to investigate the solubility in dilute ammonia. For the determination of the solubility at various temperatures a test tube and a reflux condenser were connected to a 50 cc. wide mouth flask through a rubber stopper so that the test tube was practically all below the stopper. A weighed sample of the pure ammonium monosulfonate was placed in the test tube and a burette was filled with a solution containing approximately 5% ammonia (ammonia of sp. gr. 0.882 diluted to sp. gr. 0.9770, ammonia 5.5%). The test tube was closed with a rubber stopper and an air condenser. The flask was partially filled with water and heated to boiling. Ammonia solution was run into the test tube from the burette by removing the stopper and air condenser and the apparatus shaken, using 0.1 cc. at one minute intervals near the end of the determination, until the sample just dissolved. When the solution was allowed to cool a precipitate formed within a couple of degrees showing that the solubility had not been

exceeded by any considerable amount. The temperature of the vapor of the bath was taken in each case. Ammonia boiled off from the solution so that this is not the solubility in the concentration of ammonia started with, but rather in water containing the amount of ammonia which will remain at the temperature used. This is also true of the later determinations with this apparatus since in each case addition of 5% ammonia resulted in the driving off of more ammonia gas. After cooling somewhat, the bath of water was replaced by one of alcohol and that by one of acetone. The acetone used was a technical grade and boiled slightly above the boiling point of pure acetone. An ether bath was also used but the amount of ammonia necessary was too great for accurate heating by the bath.

For determination of the solubility at room temperature a different method was employed. A sample was placed in a stoppered flask and an insufficient volumet of ammonia added, warmed and allowed to stand for a week with frequent agitation. It was then filtered. Portions of the solution were pipetted out into weighed evaporating dishes and dried at 110° to constant weight. The weight of precipitate was corrected for the water of hydration driven off in heating. Filtration to remove all the precipitate is very difficult as a small amount passes through the filter paper readily, leaving the solution slightly opalescent. The solutions used were filtered several times and were perfectly clear. The value obtained for the solubility at low temperatures is considerably less than that reported by Dreyfus and Hall,[72] 1.3 g. by extrapolation as compared with their



Solubility of Dehydro-thio-*p*-toluidine ammonium monosulfonate. At lower temperarure in 5% ammonia solution. At higher temperatures in water saturated with ammonia at the temperature of observation.

result of approximately 7 g. The results obtained are intended to represent only a rough determination of the relative solubility with change of temperature. The data obtained follow and are summarized in Fig. 3.

Temperature in ° C	Volume in cc.	Grams soluble in given volume	Grams soluble in 1 liter
100	2.6	0.1764	67.8
78.4	4.8	0.1764	36.8
58	8.6	0.1764	20.5
18.1	25.0	0.0602	2.41
18.1	35.0	0.0871	2.46

3. Dehydro-thio-p-toluidine disulfonate

Ten grams of pure dehydro-thio-*p*-toluidine (m.p. 193°, cor.) were heated with 50 g. of fuming H_2SO_4 (50% SO_3) on a boiling water bath for four hours. After cooling, the acid was added to 100 cc. of cracked ice and water and, since this did not give a precipitate, 100 cc. of saturated salt solution were added to precipitate the product. It appears to be much more soluble in water and dilute ammonia than the monosulfonate. After two recrystallizations from dilute ammonia an analysis indicated a mixture of mono- and disulfonates.

A similar procedure with eight hours' heating resulted in 5.4 g. of a pure ammonium disulfonate, yield 27.5%.

Analysis: Subs., 0.2388: $BaSO_4$, 0.3863.
Calc. for $C_{14}H_{18}N_4S_3O_6$: S, 22.02.
Found: 22.22.

The anhydrous ammonium salt is a deeper yellow than that of the monosulfonate. The ammonium disulfonate has the interesting property that in contact with the mother liquor it is practically white but on air drying it turns to a light yellow. It crystallizes from dilute ammonia with two molecules of water of hydration.

Analysis: Subs., 1.6712, 2.2094: H_2O, 0.1264, 0.1693.
Calc. for $C_{14}H_{18}N_4S_3O_6$, $2H_2O$: H_2O, 7.67.
Found: 7.58, 7.66.

4. Dehydro-thio-p-toluidine trisulfonate

A procedure similar to that for the disulfonate but heating in a metal bath at 200° for eight hours gave a product which, twice recrystallized from dilute ammonia gave two fractions in small yield. Analyses showed one of these to be pure dehydro-thio-*p*-toluidine ammonium trisulfonate, the other a mixture of di- and trisulfonates.

Analysis: Subs., 0.1912, 0.2282: $BaSO_4$, 0.3395, 0.3969.
Calc. for $C_{14}H_{21}N_5S_4O_9$: S, 24.10.
Found: 24.39, 23.89.

The anhydrous ammonium salt is a deeper yellow than that of the disulfonate. Crystallized from dilute ammonia it has three molecules of water of hydration.

Analysis: Subs., 0.1623, 0.2767: H_2O, 0.0139, 0.0256.
Calc. for $C_{14}H_{21}N_5S_4O_9$, $3H_2O$: H_2O, 9.23.
Found: 8.56, 9.25.

5. Distillation of the monosulfonate with soda lime

Ten grams of pure sulfonic acid of dehydro-thio-*p*-toluidine were intimately mixed with 10 g. of finely ground soda lime and placed in a glass retort. On heating, the distillate consisted of moisture and some red droplets soluble in HCl which gave the carbylamine test. The distillate was treated with excess of bromine water and a voluminous red precipitate obtained. This twice recrystallized from dilute alcohol with boneblack gave white needles, m.p. 120-121° (cor.). These were microscopically identical with tribromaniline prepared by direct bromination of aniline and gave a mixed melting point of 120-121° (cor.).

6. Fusion of the monosulfonate with KOH

Ten grams of KOH were fused with two cc. of water in a nickel crucible at 250-270° and 5 g. of pure ammonium sulfonate of dehydro-thio-*p*-toluidine slowly stirred in during five minutes. The melt was heated for 5 minutes longer, cooled, and dissolved in 200 cc. of water. After filtration to remove a small amount of dark precipitate the alkaline solution was carefully acidified with acetic acid and extracted with ether. The ethereal solution was extracted with sodium carbonate solution and the sodium carbonate solution acidified with acetic acid and again extracted with ether. The residue from evaporation of the ether was recrystallized from hot water with boneblacking and gave faintly yellowish crystals melting at 183° (cor.). A mixed melting point with *p*-aminobenzoic acid melting at 183° melted at 183°.

7. 2-Phenyl-5-sulfotoluthiazole

Three and a half grams of dehydro-thio-*p*-toluidine ammonium sulfonate were mixed with 125 cc. of water, acidified with two cc. of concentrated HCl and cooled to 0°. Seven-tenths of a gram of $NaNO_2$ dissolved in ten cc. of water was then slowly added with mechanical stirring, keeping the temperature below 5° at all times. The precipitate of the sulfonic acid first present appears to dissolve and the diazo compound precipitates. After testing with KI-starch paper to make sure of the presence of an excess of nitrous acid the precipitate was filtered out after one hour, washed with alcohol and then with ether and dried in air. It appeared to be stable. Yield 4 g., theoretical.

The diazo compound was converted to 2-phenyl-5-sulfotoluthiazole by boiling the above yield with 25 cc. of pure isoamyl alcohol for two hours. At the end of that time the alcohol was cooled and the precipitate filtered, washed with alcohol and finally with ether. The yield was 3.0 g., 90%. Crystallization of the ammonium salt from ammonia or from water was unsatisfactory, it proving to be practically insoluble. The product was therefore covered with concentrated ammonia and allowed to stand for two days, filtered and dried. After drying at 110° it was analyzed for sulfur:

Analysis: Subs., 0.1681: $BaSO_4$, 0.2443.
Calc. for $C_{14}H_{14}N_2S_2O_3$: S, 19.88.

Found: 19.96.

8. Fusion of 2-phenyl-5-sulfotoluthiazole with KOH

Five grams of 2-phenyl-5-sulfotoluthiazole were slowly stirred into a fusion of 10 g. of moist KOH at 270-300° and kept at that temperature for five minutes. After cooling, the melt was dissolved in 200 cc. of water and acidified with acetic acid. The dark precipitate which resulted proved to be unsatisfactory for working up for benzoic acid so the precipitate and solution were united and extracted with ether. The residue on evaporation of the ether, once recrystallized from water, was a white product melting at 120.5° (cor.), easily soluble in NaOH, slightly soluble in water and HCl. A mixed melting point with benzoic acid of melting point 121° (cor.) melted at 120.5° (cor.).

9. 2(m-Sulfophenyl)5-sulfotoluthiazole

Four and three-tenths grams of dehydro-thio-*p*-toluidine ammonium disulfonate were changed to the diazo compound by the procedure given for the monosulfonate (7). This was converted into 2(*m*-sulfophenyl)5-sulfotoluthiazole by the procedure there given, 4 g., yield 95%. The ammonium salt which is slightly soluble in water was made in the same way.

Analysis: Subs., 0.2222: $BaSO_4$, 0.3682.

Calc. for $C_{14}H_{17}N_3S_3O_6$: S, 22.91.

Found: 22.76.

10. Fusion of 2(m-sulfophenyl)5-sulfotoluthiazole with KOH

Four grams of the above compound were fused with KOH in the manner already described for the monosulfonate. The acidified solution gave practically no precipitate and extraction with ether gave only a small viscous residue. This residue and the solution were reunited and excess of bromine water added, resulting in a copious red precipitate. Twice recrystallized from dilute alcohol with boneblack this gave white needles, m.p. 95-96° (cor.). They were microscopically identical with tribromphenol and gave a mixed melting point with that substance of 95-96° (cor.).

11. Hydrolysis of dehydro-thio-p-toluidine monosulfonate to dehydro-thio-p-toluidine

Two grams of pure dehydro-thio-*p*-toluidine ammonium monosulfonate, 6 cc. concentrated HCl and 6 cc. of water were heated at 170° for 12 hours. The contents of the tube dissolved completely in NH_4OH. A similar experiment at 200° gave a small yield of dehydro-thio-*p*-toluidine, less than 5%.

As the final experiment, 1 g. of ammonium sulfonate of dehydro-thio-*p*-toluidine and 10 cc. of concentrated HCl were heated at 200-220° for 15 hours. When the tube was opened there was a small amount of black material and a yellow product, probably dehydro-thio-*p*-toluidine hydrochloride. The tube was washed out with 60 cc. of concentrated HCl and 130 cc. of water and the solution filtered. A negligible amount of black precipitate remained on the filter. 400 cc. of water were added to the acid solution and resulted in a cloudiness and small amount of precipitate, about 0.1 g. This was recrystallized from dilute alcohol and gave a few milligrams of product melting at 185° (cor.), impure dehydro-thio-*p*-toluidine. The acid solution above was neutralized with ammonia and gave a copious

white precipitate, 0.65 g. This recrystallized from a small volume fo alcohol gave 0.6 g. of dehydro-thio-*p*-toluidine melting at 191° (cor.), yield 84%. A mixed melting point of this with dehydro-thio-*p*-toluidine melting at 193° (cor.) gave a melting point of 192° (cor.).

12. Thioflavine T by direct methylation

Thioflavine T was prepared by heating 2.4 g. pure dehydro-thio-*p*-toluidine (m.p. 193°, cor.), 3 g. CH_3OH, and 1 g. concentrated HCl at 160-170° for 12 hours.[25] The dye was readily salted out, yield 3 g., 94.3%. It conformed to the usual tests[98] for Thioflavine T.

13. Thioflavine T from dehydro-thio-p-toluidine monosulfonate

Three and a half grams of pure sodium salt of the monosulfonic acid of dehydro-thio-*p*-toluidine were heated with 10 g. CH_3OH for 10 hours at 160-170°. When the tube was opened the product was white. The tube was resealed and heated at 190-200° for 12 hours longer. The product obtained is soluble in water, readily salted out and is pure white. It is probably the dimethyl-dehydro-thio-*p*-toluidine sodium monosulfonate, the analogue of Thioflavine S.

One gram of dehydro-thio-*p*-toluidine sodium monosulfonate, 2 cc. of methanol and 10 cc. of concentrated HCl were heated at 200-220° for 12 hours. The tube had a high pressure of inflammable gas. The substance formed a ruby-red liquid with a very small amount of red precipitate. This, when diluted with water gave a red precipitate. The solubility in water was moderate in the cold, quite soluble in hot. The precipitate obtained was washed well with water and dried, weight 1.2 g., theoretical yield would be 0.90 g. A dyeing test was made with the above and gave on silk a beautiful yellow which differed slightly in quality from that of Thioflavine T by direct methylation.

A similar experiment was run using the ammonium monosulfonate. The reactions here mentioned are difficult to carry out in glass bombs because of building up of a great deal of pressure. That was illustrated in the case of this experiment, which ran for 12 hours at 200-220° safely but which, after cooling over night, exploded violently when the capillary was warmed to open it, blowing the larger portion of the tube to bits inside of the protecting iron tube. A portion of tube about six inches long remained and contained a sufficient amount of dye for a dyeing test. The test did not differ from that with the sodium salt.

14. Columbia Yellow

Columbia Yellow was prepared according to German patent 65,402,[56] using chloride of lime and soda, PbO_2, and $K_3Fe(CN)_6$ as oxidizing agents. Oxidation with an accurately titrated solution of NaOCl made by passing chlorine into NaOH solution[85] was found most satisfactory in quality[97] and yield.

15. Benzal-dehydro-thio-p-toluidine

Ten and six-tenths grams of benzaldehyde were dissolved in 25 cc. of alcohol. Twenty-four grams of dehydro-thio-*p*-toluidine were dissolved in 225 cc. of hot alcohol and the solution containing the benzaldehyde slowly added.[91] After boiling gently for two hours it was poured through a

filter and crystallized on cooling. The crude product weighed 31.2 g. and melted at 183° (cor.). This, once recrystallized from alcohol, melted at 188° (cor.), 27.1 g., 82.7%. Further recrystallization from alcohol raised the melting point to 192° (cor.); M. Meyer[89] found 193°.

The compound was analyzed by fusion with KNO_3 and mixed carbonates

Analysis: Subs., 0.2000: $BaSO_4$, 0.1422.

Calc. for $C_{21}H_{16}N_2S$: S, 9.76.

Found: 9.76.

Because of its later use the stability in the presence of acid was tested.[59, 61] Two grams benzal-dehydro-thio-*p*-toluidine were placed in a flask and 20 cc. of concentrated HCl and 40 cc. of water added. The odor of benzaldehyde was clearly discernible on adding the acid. Steam was blown through for one-half hour. When cooled, neutralized with ammonia and filtered, 1.5 g. of residue were obtained, theoretical 1.46 g. Recrystallized from alcohol it melted at 193° (cor.) and had the crystalline form of dehydro-thio-*p*-toluidine.

16. Attempts to convert benzal-dehydro-thio-p-toluidine to a pseudo primuline

Benzal-dehydro-thio-*p*-toluidine and sulfur were fused in theoretical proportions at temperatures from 200° to 240°. Variations of proportions with each component in excess were also tried.

H_2S was evolved. Investigations of the melts with solvents failed to show the presence of the desired product. Vacuum distillation yielded only sulfur and traces of low-melting impurities. By decomposition with HCl all but 0.7 g. of a 10 g. portion of crude melt made with theoretical proportions was shown to consist of dehydro-thio-*p*-toluidine or the benzal derivative.

17. Benzoyl-dehydro-thio-p-toluidine

Twenty-four grams of dehydro-thio-*p*-toluidine were dissolved in 500 cc. of hot alcohol and 16 g. benzoyl chloride, dissolved in 50 cc. of alcohol, added. The boiling was continued under a reflux as the precipitate gradually formed until after one minute the flame had to be removed because the precipitate formed a semi-solid mass. After standing for two hours to cool and complete the reaction the mass was washed onto a filter with alcohol, washed with alcohol and dried, yield 33.3 g. of crude, 96.8% with a melting point of 243.5-244° (cor.). The substance is then a lemon-yellow to orange. After washing with cold normal NaOH solution, one crystallization from alcohol in which it is only slightly soluble hot and practically insoluble cold, with boneblacking, gives it as very light yellow needles, m.p. 244.4° (cor.). Condensation in acetone gave a yield of 93%.

Benzoyl-dehydro-thio-*p*-toluidine is slightly soluble in hot acetic acid and acetone, less in cold; slightly soluble in chloroform, amyl alcohol, and toluene, very slightly soluble in ether; slightly soluble in dilute HCl, reprecipitated by NH_4OH; very soluble in nitrobenzol.

Three successive recrystallizations showed the melting point of 244.4° (cor.) to be constant and the sample so obtained was analyzed (Carius).

Analysis: Subs., 0.1839: $BaSO_4$, 0.1284.

Calc. for $C_{21}H_{16}N_2OS$: S, 9.30.

Found: 9.59.

Its stability to acids and alkalies was investigated. Three and a half grams were treated with 30 cc. of concentrated HCl, 5 cc. of alcohol, and 60 cc. of water. This was heated to boiling and steam blown through for 45 minutes. Much precipitate remained. When filtered and the filtrate precipitated by ammonia, little precipitate was obtained. A portion of the main precipitate of 3.5 g. when recrystallized proved to be the starting material.

A two gram sample was boiled with normal NaOH for 2 hours. The white precipitate which remained weighed 2 g., melted at 244.4° (cor.) and once recrystallized from alcohol gave the same melting point. The filtrate gave no precipitate when neutralized with HCl.

18. Attempt to prepare pseudo primuline from benzoyl-dehydro-thio-p-toluidine

Six and nine-tenths grams of pure benzoyl-dehydro-thio-*p*-toluidine were fused with 0.7 g. of sulfur, the theoretical quantity, for three hours. Since the melting point of the starting materials is so high it was necessary to carry the temperature to about 250° in order to obtain a satisfactory fusion. H_2S was evolved. Extraction of the melt did not indicate the presence of any considerable amount of starting material.

The residue of 4.2 g. could not be recrystallized from alcohol, amyl alcohol, aniline, nitrobenzol or glacial acetic acid. Suspended in the nitrobenzol solution it appeared to exist as well defined crystals and under the microscope appeared to be present as fine flakes. It does not melt but sinters above 350°. From this it did not seem probable that it was pseudo primuline so the residue was not further investigated.

19. Reaction of dehydro-thio-p-toluidine with hydroquinone and attempt at a dye analagous to hydrone blue

Twenty-four grams of dehydro-thio-*p*-toluidine (m.p. 193°, cor.) were heated with 15 g. of hydroquinone and one cc. concentrated H_2SO_4 in an atmosphere of CO_2 for four to five hours at 220-240°.[60] At the end of the reaction, indicated by the solubility of a test portion in dilute NaOH, the melt was poured into water and gave a black glassy mass. This is soluble in NaOH and precipitated by HCl, to give about 10 grams of a dark brown substance. This was dissolved in hot glacial acetic acid and filtered. On cooling a black material crystallized out. The solution was then filtered and the filtrate diluted with water. The yellow precipitate which came down is analagous to a product obtained with resorcinol.[60] The melting point was very low, 140-160° in different lots, yield not over 3 grams.

The yellow product did not crystallize well from toluene, alcohol or xylene and could not be sufficiently purified to give a constant melting point or to warrant analysis.

The crude yellow product of the preceding reaction was treated as in the production of hydrone blue,[68, 69] with negative results.

20. Di-dehydro-thio-p-toluidine thiourea

Twenty-four grams of pure dehydro-thio-*p*-toluidine (m.p. 193°, cor.)

were refluxed with 25 cc. CS_2 and 100 cc. of acetone for 8 hours. On filtration 12 g. of crude product were obtained. After standing for 3 weeks there had been deposited 12 g. more of product and on standing for another week 2 g. more of product were deposited, yield 98%. The above crude product was boiled with 250 cc. of alcohol for an hour and filtered hot. The filtrate gave a very faint fluorescence of dehydro-thio-*p*-toluidine and the loss of weight of the precipitate was negligible.

The thiourea is insoluble in all low boiling solvents such as alcohol, ether, chloroform, CS_2, petroleum ether, acetone, etc. It was recrystallized from nitrobenzol but the color became darker and successive recrystallizations gave lower melting points. This product from nitrobenzol was extracted with alcohol and gave a solution with a greenish fluorescence which, when concentrated, deposited crystals melting at 191° (cor.) and identical in crystalline form with dehydro-thio-*p*-toluidine. Similar results were obtained in attempts to recrystallize from napthalene and ethyl benzoate. It therefore appears that decomposition takes place in such high boiling solvents.

The product obtained by extraction with alcohol or acetone exists as irregular light yellow microscopic plates melting at 238.2° (cor.). This is above the best obtainable by recrystallization from any of the above solvents. After three extractions with alcohol it was analyzed.

Analyses: Subs., 0.2053: CO_2, 0.5017; H_2O, 0.0788.
Subs., 0.1935, 0.1374: $BaSO_4$, 0.2614, 0.1795.
Calc. for $C_{29}H_{22}N_4S_2$: C, 66.66; H, 4.21; S, 18.39.
Found: C, 66.65; H, 4.29; S, 18.55, 17.94.

An attempt was made to recrystallize from aniline. The products obtained were dehydro-thio-*p*-toluidine, m.p. 191° (cor.), and thiocarbanilid.

Five and two-tenths grams of the thiourea were boiled with 10 cc. of aniline and 25 cc. of toluene for 3 hours, at the end of which time all had dissolved. When filtered into a crystallizing dish 4 g. of dehydro-thio-*p*-toluidine crystallized, m.p. 186-188° (cor.), 83%. Recrystallized once from alcohol it gave 2.4 g. purified dehydro-thio-*p*-toluidine, m.p. 193° (cor.), 50%. The filtrate was diluted with water, a drop of NaOH added and the aniline and toluene steam-distilled. From the residue of 2.5 g., 1 g. of thiocarbanilid, 44%, was extracted with hot water, and recrystallized from dilute alcohol, m.p. 152°. A mixed melting point with thiocarbanilid prepared according to the method of Hofmann[2] melting at 154°, was 153°. From the residue another product was isolated melting about 220°. This was not studied further.

A similar reaction was carried out with 5.22 g. of di-dehydro-thio-*p*-toluidine thiourea, 15 cc. of *o*-toluidine and 25 cc. of toluene. It was necessary to heat for 20 hours to complete the reaction. Four and two-tenths grams of dehydro-thio-*p*-toluidine were obtained which, recrystallized from alcohol, gave 4.0 g. of m.p. 193° (cor.), 83%. The filtrate was diluted with water and steam-distilled to remove the toluidine and toluene. The aqueous solution deposited some crystals on cooling. These were

joined with the residue and recrystallized from alcohol. After two recrystallizations from alcohol there remained 1.9 g. of di-*o*-tolylthiourea melting at 163-164° (cor.), 74%. Berger[9] reports the melting point as 158° and Girard[5] as 165°.

Attempts to prepare a mustard oil from this thiourea by the use of either phosphoric or sulfuric acid were unsuccessful.

21. o-Dinitrophenyldisulfid

This was prepared according to Wohlfahrt.[68] Yields were as reported, about 75%, m.p. 195° (cor.).

22. Zinc salt of o-aminothiophenol

Three and one-tenth grams of dinitrophenyldisulfid were dissolved in 350 cc. of glacial acetic acid by warming, and zinc dust added in small portions. For rapid reduction (30 min.) about 20 g. were used although 5 g. would give reduction after a time. In either case the solution was boiled until colorless and filtered. If allowed to crystallize on standing the product is impure and must be well washed with water to remove inorganic salts. This solution becomes supersaturated unless frequently stirred. If the acetic acid solution is diluted with two volumes of water, practically pure zinc salt of the thiophenol is obtained on filtration, yield 2.8 g., 90%. For analysis samples were ignited to the oxide.

Analyses: Subs., 0.8738, 1.5416; ZnO, 0.2294, 0.3976.
Calc. for $C_{12}H_{12}N_2S_2Zn$: ZnO, 25.93.
Found: 26.25, 26.11.

23. 2-Phenylbenzothiazole from the zinc salt of o-aminothiophenol

Three and two-tenth grams of pure zinc salt of *o*-aminothiophenol were heated to boiling with 3 g. of benzoyl chloride for a half hour. The fusion was extracted by warming with excess of N NaOH, filtered and recrystallized from 50% alcohol with boneblacking, yield 4 g., 94%. The melting point was 114° (cor.), a mixed melting point with some prepared in another way,[94] 114° (cor.). The loss is largely in recrystallization.

24. 2(p - Nitrophenyl)benzothiazole

Three and two-tenths grams of pure zinc salt of *o*-aminothiophenol were heated with 3.7 g. of *p*-nitrobenzoyl chloride in a test tube on a boiling water bath for one hour. The fusion was extracted by warming with excess of N NaOH, filtered and recrystallized from a large volume of alcohol with boneblacking, yield 3.6 g., 70%.

The substance crystallizes as very small light yellow needles melting at 231° (cor.), easily soluble in concentrated HCl, precipitated as a very light yellow flocculent precipitate by dilution ;slightly soluble in hot alcohol and acetone, very slightly soluble in cold; soluble in hot amyl alcohol, slightly soluble in cold; soluble in hot acetic acid, moderately soluble in cold; soluble in chloroform; insoluble in ether, benzol, and carbon tetrachloride.

Analysis: Subs., 0.1893: $BaSO_4$, 0.1720.
Calc. for $C_{13}H_8N_2O_2S$: S, 12.50.
Found: 12.47.

25. 2(p-Aminophenyl)benzothiazole from 2(p-nitrophenyl)benzothiazole

Two and six-tenths grams of 2(*p*-nitrophenyl)benzothiazole were boiled with five cc. of concentrated HCl, 95 cc. of water, and 10 g. of granulated tin for three hours. The substance had all gone into solution at the end of two hours. When filtered, a precipitate forms on cooling. The acid solution was made strongly alkaline with 4N NaOH, kept warm for an hour, cooled, and filtered. Recrystallized from 50% alcohol with boneblacking, it melts at 155° (corr), yield 2 g., 90%. The melting point previously reported[71] was 155°. The product crystallizes as very light yellow needles. It shows a blue fluorescence in alcoholic solution and is slightly soluble in warm water.

Analysis: Subs., 0.2010: $BaSO_4$, 0.2103.
Calc. for $C_{13}H_{10}N_2S$: S, 14.16.
Found: 14.35.

26. Di-o-aminophenyldisulfid

Three and two-tenth grams of finely powdered pure zinc salt of *o*-aminothiophenol were placed in a gas wash-bottle, 50 cc. of concentrated ammonia solution and an equal volume of water added. Air was drawn through for two hours during which the white particles of zinc salt gradually dissolve and a crystalline precipitate of the disulfid forms. Filtered and recrystallized from 25% alcohol with boneblacking it appears as lustrous light yellow plates, m.p. 93°,[10] yield 1.6 g., 65%. The loss in recrystallization is large.

27. Bis(o-benzoylaminophenyl)disulfid

Two and a half grams of di-*o*-aminophenyldisulfid were heated with 3 g. benzoyl chloride on a boiling water bath for one hour. The fusion was extracted with excess of N NaOH, filtered and recrystallized from 50% alcohol with boneblacking, yield 3.8 g., 83%.

The product crystallizes as long white needles melting at 142.6° (cor.). In hot alcohol, amyl alcohol, carbon tetrachloride, acetone and acetic acid it is very soluble, and moderately soluble in cold; moderately soluble in carbon disulfid and benzol; easily soluble in chloroform and toluol; insoluble in ether.

Analysis: Subs., 0.1706: $BaSO_4$, 0.1779.
Calc. for $C_{26}H_{20}N_2S_2O_2$: S, 14.03.
Found: 14.32.

28. 2-Phenylbenzothiazole from bis(o-benzoylaminophenyl)disulfid

Two and three-tenth grams of bis(*o*-benzoylaminophenyl)disulfid were boiled with five cc. of concentrated HCl, 95 cc. of water, and 10 g. of granulated tin for fifteen minutes. Solution occurs in about five minutes. The acid solution was made strongly alkaline with 4N NaOH, kept warm for an hour, cooled, and filtered. Recrystallized from 50% alcohol it melted at 114° (cor.), yield 1.9 g., 90%. A mixed melting point with some prepared by another method[94] melted at 114° (cor.).

29. Bis(o-p-nitrobenzoylaminophenyl)disulfid

Two and a half grams of di-*o*-aminophenyldisulfid were dissolved in 10 cc. of anhydrous ether. Three and seven-tenth grams of *p*-nitrobenzoyl

chloride were dissolved in 40 cc. of anhydrous ether by warming. Immediate precipitation occurs on mixing the two solutions. After standing for fifteen minutes the precipitate was filtered and dried and recrystallized from a large volume of alcohol, yield 4 g., 73%. This melted at 213° (cor.) with decomposition. Further recrystallization raised the melting point to 217° (cor.) with decomposition. The solubilities are about the same as those of 2(*p*-nitrophenyl)benzothiazole except in concentrated HCl in which this compound is practically insoluble.

Analysis: Subs., 0.1988: $BaSO_4$, 0.1677.
Calc. for $C_{26}H_{18}N_4S_2O_6$: S, 11.72.
Found: 11.58.

30. 2(p-Aminophenyl)benzothiazole from bis(o-p-nitrobenzoylaminophenyl) disulfid

Two and eight-tenths grams of bis(*o*-*p*-nitrobenzoylaminophenyl) disulfid were boiled with 10 cc. of concentrated HCl, 10 cc. of water and 10 g. of granulated tin for four hours. The substance had all dissolved at the end of three hours. The solution was diluted with 150 cc. of water and filtered. The acid solution was made strongly alkaline with 4N NaOH, kept warm for an hour, cooled and filtered. Recrystallized from 50% alcohol the product melts at 155° (cor.),[71] yield 2.1 g., 80%. Mixed with some prepared by the other method (see 25) it melted at 155° (cor.).

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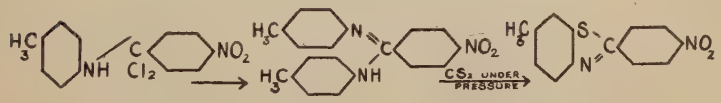
BIOGRAPHICAL

Foster Dee Snell was born in Binghamton, New York, on June 29, 1898. After attending the high school of that city he entered Colgate University in 1915. He received the degree of B. S. in 1919 from that institution. From 1919 to the present he has been studying under the Faculty of Pure Science of Columbia University from which he received the degree of M. A. in 1922.

He is the author of "Colorimetric Analysis" (D. Van Nostrand Company), published in 1921. As an instructor in chemistry at the College of the City of New York for the past three years, he now has the rank of tutor. He is a member of the American Chemical Society and of Sigma Xi.

Errata

Page 10. Five lines from bottom. Replace Formula V by the following:



Page 11. Line five. Insert Formula V from page 10.